REMARKS

Claims 28-33, 54-88, and 93-104 constitute the pending claims in the present application.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the Office Action.

Claim rejections under 35 U.S.C. 112, first paragraph

Claims 28-33, 54-88, and 93-104 remain rejected under 35 U.S.C. 112, first paragraph, for failing to comply with the enablement requirement.

Specifically, the Office Action asserts that Applicants has argued the definition of SA as "carrier protein" as defined by page 10 of the specification, thus the argument still fails to address the core issue of "increased biological activity." The Office Action further asserts that "[f]or the art search purpose of this Office Action, the Office will assume that that increased half-life is increased biological activity in view of applicants' argument that albumin is a carrier protein, which suggests [sic] has same meaning, i.e., increased plasma stability."

First of all, assuming the Office Action means "increased half-life" has the same meaning as "increased biological activity," Applicants note a major shift of force of argument regarding 35 USC 112, first paragraph. In the previous Office Action issued by the previous Examiner, the rejection was based on the Examiner's mis-interpretation of requiring the "heterologous peptide sequence" to share less than 40% identity with the SA. No issues regarding "the increased biological activity" were ever raised in the previous Office Action.

Secondly, Applicants respectfully disagree that "increased stability (half-life)" is the same as "increased biological activity." One significant difference between "increased biological activity" and "enhanced stability" is that the former usually requires the polypeptide to have some kind of biological activity of its own (such as being able to act on a target molecule), while the latter simply requires the polypeptide to be stable. In an extreme example, a randomly synthesized peptide may not have any kind of biological activity, but it can be quite stable in solution. Thus, equating "increased biological activity" with "increased serum half-life," as the Office Action suggests, seems to be unwarranted.

Applicants submit that an apparent observed increased biological activity as taught in the present specification is likely to result from factors apart from increased serum half-life. For

example, by stabilizing the structure of the inserted heterologous polypeptide in a favorable conformation, the inserted heterologous polypeptide may be qualitatively more active than its free form. For example, page 44, 2nd full paragraph of the instant specification teaches that "[t]he insertion of the EC binding peptides into MSA increased their inhibitory activity by approximately 1000-fold." This dramatic increase in biological activity of the subject EC-binding peptides is presumably due, at least in part, to their conformation as part of the serum albumin fusion proteins. In other words, the dramatic increase in biological activity is not likely to be fully accounted for by the possible increase in serum half-life. In fact, this increased biological activity is particularly likely due to a qualitative activity change other than a simple half-life increase, considering the fact that the SA chimera and the uninserted heterologous peptide probably have very similar half-lives in tissue culture conditions, since there are not as many destabilizing factors such as proteases in tissue cultures as in serum.

In addition, the EC-binding peptide data presented in the specification directly refutes the assertion of the Office Action that "the specification does not teach any biological activity of a peptide increased other than serum albumin being used as carrier protein."

For example, the specification indicates, on page 44, second paragraph, that the EC binding peptides inserted into mouse serum albumin actually exhibit 1000-fold more activity than the uninserted synthetic peptides themselves. The chimeric polypeptide is effective in inhibiting EC cell proliferation at nanomolar concentrations, while the uninserted peptide is effective only in the millimolar range.

Lastly, the standard for enablement is whether a skilled artisan, in view of the teaching of the specification and common knowledge, would be able to practice the claimed invention without undue experimentation. Factors to be considered in assessing enablement are set forth in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Applicants submit that the instant claimed invention is fully enabled, as is evidenced by the EC-binding peptides tested in the Example. A skilled artisan would need no undue experimentation to insert heterologous polypeptides into the SA according to the teachings of the instant specification. And the skilled artisan would have no difficulty comparing the half-lives and biological activities of inserted and uninserted heterologous peptides.

Therefore, based on the above argument, Applicants submit that all pending claims meet the requirement of 35 U.S.C. 112, first paragraph. Reconsideration and withdrawal of the rejection is respectfully requested.

Claim rejections under 35 U.S.C. 102

Claims 28, 54, 55-77, and 93-104 are rejected under 35 U.S.C. 102(b), as being anticipated by WO 95/30759 ("'759" thereafter) as evidenced by Zetter and by Fixe.

Specifically, the Office Action asserts that '759 teaches that chimeric polypeptide with a useful heterologous peptide inserted anywhere within serum albumin (SA) can be derived from various therapeutically useful proteins, including an angiogenesis-inhibiting protein or a protein that binds to receptor tyrosine kinase (RTK). The '759 application also allegedly teaches chimeras with increased *in vivo* stability. The Office Action acknowledges that '759 does not specify the functional property of the various useful proteins, a laundry list of functional properties are listed in pages 3 and 4, also in claim 3 of '759. Thus the Office Action concludes that the functional properties are inherent properties of the useful proteins. To support this, the Office Action also refers to Fixe to show that it was well known in the art that M-CSF is a RTK (note: should be "ligand for RTK"), and that an active portion of M-CSF inserted into the SA protein would bind to a cell surface receptor or RTK. Similarly, the Office Action refers to Zetter which shows that angiostatin and endostatin are well known in the art as angiogenesis-inhibiting proteins useful for cancer treatment.

Applicants submit that the claimed invention is a chimeric SA polypeptide that "exhibits increased biological activity to the heterologous peptide sequence itself" (emphasis added). The instant specification teaches that the chimeric polypeptide of the claimed invention exhibits increased biological activity when compared to the uninserted heterologous peptide itself. As explained before, "increased biological activity" is not the same as "enhanced stability." Thus '759 fails to teach each and every aspect of the claimed invention, and cannot anticipate the claimed invention.

As argued before, the specification indicates, on page 44, second paragraph, that the EC binding peptides inserted into mouse serum albumin actually exhibit 1000-fold more activity than the uninserted synthetic peptides themselves. The chimeric polypeptide is effective in inhibiting EC

cell proliferation at nanomolar concentrations, while the uninserted peptide is effective only in the millimolar range. In contrast, '759 is completely silent about increased biological activity. It merely *hoped* that a chimeric polypeptide might possess enhanced stability, which '759 never shows (Applicants note that Example 8 only shows that an inserted short peptide is *accessible* to a protease, but is otherwise completely silent on the stability of the chimeric peptide as compared to the uninserted short peptide itself – such comparison is simply never made. Plus, the ability to serve as a protease substrate cannot be interpreted as a "biological activity").

Even assuming, for the sake of argument, that what the '759 application suggests is true, enhanced stability is still quite different from increased biological activity, as claimed in the instant application. As a skilled artisan would appreciate, two otherwise identical polypeptides may have the same stability (for example, life-span in serum), but can have dramatically different overall biological activities, no less potencies, due to factors such as conformation in a specific solution. Another distinction between "increased biological activity" and "enhanced stability" is that, the former usually requires the polypeptide to have some kind of activity of its own (such as being able to act on a target molecule), while the later simply requires the polypeptide to be stable (see above).

The '759 application also fails to describe any assay or even an intention of comparing biological activity between the inserted heterologous peptide and the uninserted counterpart, thus failing to put the claimed invention in possession of the public, as is legally required for anticipation (see below). Reference to Zetter or Fixe does not correct this defect.

Also, Applicants have never conceded that the '759 application actually shows increased stability (see above and more below), nor equated "increased half-life (stability)" to "increased biological activity." In arguments filed with the previous response, Applicants' position is that the examples of the instant specification demonstrate that cysteine loops of SA provide an effective "expression cassette" which allows the expression of such "active heterologous peptides" with increased stability, and retained/increased potency (see above). Therefore, "increased potency" is recited in addition to "increased stability." Applicants have clearly conveyed the idea that increased biological activity may not be fully accounted for by increased stability alone (also see below).

Lastly, claims 28, 54, and 55 of the instant application unambiguously recite that "the chimeric polypeptide exhibits increased biological activity relative to said peptide sequence itself."

This feature is clearly present in all pending claims, but neither taught nor suggested in the '759 application.

Applicants further submit that '759 fails to inherently anticipate the claimed invention. Pursuant to MPEP 2112, "Examiner must provide rationale or evidence tending to show inherency." The same section of MPEP further states that "[t]he fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)," (emphasis in original), and that "[i]n relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.' *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)."

The '759 application at best hoped for a serum albumin chimera with enhanced half-life with regard to the inserted heterologous polypeptide, while its only "working example" does not even show the enhanced half-life, nor can it be argued that being a protease substrate is a "biological activity." The '759 application at best enables a skilled artisan to make and use a chimera of enhanced half-life (assuming measuring half-life of a protein was common knowledge in the art at the time of filing), but does not teach or suggest that an inserted heterologous polypeptide may exhibit an *unexpectedly increased* biological activity. In other words, the potentially "inherent characteristic" – increased biological activity – does not *necessarily* flow from the disclosure of '759, and a skilled artisan would never have expected that an inserted heterologous polypeptide may have increased biological activity. Thus '759 fails to inherently anticipate the claimed invention.

"Anticipation" in the patent sense means that the subject matter was previously known. The claimed invention is partly based on the unexpected result of the inserted heterologous peptide exhibiting increased activity. Thus, '759 cannot anticipate the claimed invention, which is a species of SA chimera with a unique and unexpected property within a genus of SA chimeric polypeptides. Until Applicants demonstrated that chimeric albumins as claimed can indeed exhibit increased biological activity, a skilled artisan never would have reasonably expected this result, even had it been desired.

Therefore, the '759 application does not teach or suggest each and every aspect of the claimed invention, and cannot anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Claim rejections under 35 U.S.C. 103(a)

Claims 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over '759 as applied to claims 28, 54, and 55 above, further in view of the specification at pages 16-22.

The Office Action asserts that the specification admits that the various vectors and cells are well known, and since the specification does not teach unexpected results using the recited vectors and cells, it is obvious variation of the vectors and cells taught by the primary references.

Claims 29-33 are directed to delivery vectors and transfected cells comprising the nucleotide of claim 28, thus these claims are non-obvious if claim 28 is non-obvious. Applicants submit that the claimed invention is non-obvious over the '759 application, since the '759 application never teaches or suggests that an inserted heterologous polypeptide actually may have increased biological activity as taught in the instant specification. In fact, the 1000-fold increase of biological activity of the EC binding peptides is a dramatic increase in activity, and is an unexpected result that cannot be readily predicted based on the collective teaching of any cited prior art references.

Claims 80-84 are rejected under 35 U.S.C. 103(a) as being unpatentable over '759 as applied to claims 28, 54, and 55 above, further in view of Cardarelli.

Specifically, the Office Action asserts that the claimed invention recites "at least two inserted heterologous polypeptides," which is allegedly an obvious variation of the cited primary reference disclosure "at least one active" heterologous polypeptide, since applicants do not show any unexpected results. Further, Cardarelli teaches "RGD is well known in the art."

As argued above, claim 80 and its dependent claims also contain the "increased biological activity" feature, which is not taught or suggested by any of the cited references or combinations thereof, assuming for the sake of argument, that such combination would be made by a skilled artisan. Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 85-88 are rejected under 35 U.S.C. 103(a) as being unpatentable over '759 as applied to claims 28 above, further in view of Carter *et al.*

Specifically, '759 allegedly teaches that any therapeutically desirable peptide can be inserted into any location within SA. However, the Office Action acknowledges that '759 does not specifically teach insertion of the heterologous peptide into a portion of a Cys loop of a SA protein. The Office Action also alleges that '759 teaches in Figure 1 that SA has extensive Cys loops, and that Carter teaches the crystal structure of SA with "several surface exposed cysteine loops (see page 167-173)." The Office Action contends that, since the specification does not teach any unexpected results with the specific cysteine loops, which are already known in the art, it is an obvious variation of the teaching of the primary references.

Pursuant to MPEP 2142, "[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. Using the Applicants' disclosure as a template for picking and choosing from amongst the prior art to reconstruct the claimed invention is not permitted. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)." Thus, to render the claimed invention obvious, all three criteria must be met.

Regarding the insertion site, the '759 application suggests that the heterologous peptide may be inserted into sites that "are preferably localized in the regions of the albumin presumed to form exposed regions at the surface of the molecule, these regions preferably being loops" (page 7, lines 3-5). However, contrary to the Office Action's assertion, the '759 application never teaches or suggests that any of these sites could be cysteine loops as claimed in the instant application. In fact, the '759 application does not refer to any cysteine loops at all. Instead, the '759 application suggested a few preferred insertion sites as "residues 57-62 (region 5) which corresponds to a loop connecting helices h3 and h4; residues 103-120 which corresponds to the zone between subdomains (region 8, an alpha helix structure, not a loop at all); residues 178-200 which corresponds to a helix (region 13, another alpha helix, not a loop at all); and residues 419-430 which corresponds to a region defined by helices h2 and h3 of domain III (not a Cys loop). Aside from region 5, which partially overlaps with one of the claimed Cys loops, none of these preferred sites actually corresponds to any of the claimed Cys loops. Even though the '759 application suggests that the

insertion sites are preferably exposed surface loops, there are many different surface loops in the SA structure. This genus of "exposed surface loop structure" does not anticipate the claimed Cys loops, one particular species of the exposed surface loops. Neither would this genus of loops specifically suggest that a skilled artisan look for Cys loops on the surface of SA. The advantage of the Cys loop, first recognized by the present inventors, partly resides in the fact that these loops are structurally constrained by the disulfide bonds forming these loops, and thus a peptide inserted within the Cys loop is much less likely to disrupt the overall structure of the chimeric protein, while a peptide inserted in a non-constrained loop or helix structure are more likely to disrupt the overall structure and/or stability of the chimera. This concept was neither taught nor suggested by the '759 application. In fact, Figure 1 of '759 actually shows many potential loop-like structures between the helices. These loops are not necessarily linked by disulfide bonds (see, for example, the loops between h2 and h3, between h6 and region 8, between region 8 and h7, etc.).

On the other hand, Carter is a review article relating to the structure of SA. In the passage cited by the Office Action (pages 167-173, especially Figure 10 and Table II), Applicants were unable to find any specific reference to "surface exposed cysteine loops," as recited in the Office Action. The only passages relating to the "Cys loop" seem to be descriptions for "disulfide bridges" (see page 169, last line; several occurrences on page 170; and page 171, section "b"). But none of these passages seems to indicate that any Cys loops are actually "surface exposed," let alone suitable to serve as potential insertion sites for heterologous proteins. Thus, Carter also does not suggest Cys-constrained surface-exposed loops claimed in the instant application. Applicants respectfully request that the Examiner point out / recite specific sentences or passages from Carter which clearly indicate that serum albumin has several "surface exposed cysteine loops" as recited in the Office Action.

In view of this, even if a skilled artisan is motivated to combine '759 and Carter, the artisan would not specifically look for Cys loops as claimed in the instant application. Thus the combined teachings of '759 and Carter still fail to guide a skilled artisan to arrive at the claimed invention, and do not teach or suggest all the limitations of the claimed invention.

Applicants further submit that a skilled artisan would also lack a reasonable expectation of success in arriving at the claimed invention (chimeric SA polypeptide containing a heterologous polypeptide inserted into the Cys loop(s) and with an increased biological activity).

As argued above, the cited art disclosed fusion of heterologous peptides to either the N- or C-terminus of SA, but, except for the '759 application, not insertion of heterologous peptides into the SA. However, none of these references teaches or suggests that an inserted heterologous peptide may have *increased* biological activity compared to the uninserted counterpart. Thus, a skilled artisan would have no reasonable expectation that an inserted heterologous peptide would actually show *increased* biological activity. Indeed, the *increased* biological activity is an unexpected result that is not obvious in view of the prior art teaching.

Accordingly, despite the generic teachings of the '759 application, a skilled artisan would have had no reasonable expectation of success in arriving at the claimed invention. In other words, until Applicants demonstrated that the chimeric albumins could indeed exhibit dramatic (in the present case, about 1000-fold) increase in biological activity, *a priori*, one of ordinary skill in the art would not have had a reasonable expectation for success based on the teachings of the '759 application and the knowledge available in the prior art. In addition, the skilled artisan would also lack motivation to pick the Cys loops recited in the claims, and insert heterologous peptides into these constrained Cys loop sites, since the natural conformation of the inserted peptide might be too distorted to maintain activity.

In view of the foregoing, Applicants submit that all three requirements for making a *prima facie* case of obviousness are not met. Accordingly, reconsideration and withdrawal of rejection under 35 U.S.C. 103(a) are respectfully requested.

Double Patenting Rejections

The Office Action states that claims 28-33, 54-84, 93-104 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 28-33, and 49-91 of the co-pending U.S. Application 09/619,285.

Applicants submit that, pursuant to MPEP 804, "[i]f the 'provisional' double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent [without filing a terminal disclaimer], thereby converting the 'provisional' double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent."

If conflicting claims are first allowed in the co-pending U.S. Application 09/619,285 and appear in an issued U.S. patent, Applicants note that, pursuant to 37 CFR 1.130(b), a timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome the double patenting rejection. Applicants will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

If there are any other fees due in connection with the filing of this submission, please charge the fees to our **Deposit Account No. 18-1945.** If a fee is required for an extension of time under 37 C.F.R. § 1.136 not accounted for above, such an extension is requested and the fee should also be charged to our Deposit account.

Respectfully Submitted,

Date: August 19, 2003

Customer No: 28120
Docketing Specialist
Ropes & Gray, LLP
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050

Yu Lu, Ph.D.
Patent Agent
Reg. No. 50,306